REMARKS/ARGUMENTS

I. Status of claims

Claims 16, 22, 26, 30, 34, 38, 42, 46, 50 and 54 are amended.

Claims 5-9 were withdrawn previously as they referred to non-elected species. Applicants reserve the right to rejoin these claims if the elected species are found to be allowable.

Claims 1-4, 10-57 are being examined.

Support for the claim amendments can be found at least in the original claims 11-13 and paragraph [0018] of the specification.

II. Benefit of Priority Extends to the Filing Date of the Provisional Application.

The examiner alleges that the provisional application does not comply with the requirements of 35 U.S.C. §112 first paragraph because the examiner believes that the provisional application "does not describe anything related to using said cell line to inducing [*sic*] immune response to treat and prevent any of [*sic*] cancer associated and non-associated with EBV infection". (page 3, Office Action).

The pending method claims do not relate to "cancer ... non-associated with EBV infection" as the examiner alleges. The provisional application as filed describes "treating patients with cancer", "EBV-associated malignancies", and "cell vaccines for treating EBV (+) tumors" under the Abstract as well as the Detailed Description sections of the application.

Therefore, the provisional application adequately supports claims 4, and 16-57 under 35 U.S.C. §112 first paragraph requirements. Applicants request the examiner to accord benefit of priority of the filing date of the provisional application 60/411,990, filed September 19, 2002.

III. Claims 16-57 satisfy 35 U.S.C. §112 first paragraph enablement requirement.

The Examiner on page 3 of the Office Action rejected claims 16-57 for lack of enablement because the Examiner believes that it would require undue experimentation to practice the claims.

The Examiner acknowledges:

> It is also well know [*sic*] in the art that cancers/tumors are caused or developed by many different mechanisms and/or different cancer/tumor related gene expressions as evidenced by Nawrocki et al. (Cancer Treatment Reviews, Vol. 25, No. 1, February 1999, Pages 29-46). Not all cancers/tumors are related to the EBV infection.

Page 4, Office Action.

However, the Examiner, without support concludes:

> Therefore, it is unpredictable that the [*sic*] administering the claimed human cell line is able to produce a prophylactic immune response to any or all kinds of cancers or tumors before the person infected [*sic*] with an EBV infection.

Page 4, Office Action.

The examiner has not provided any specific evidence to show that the claimed methods would not work, but merely offers a general statement on unpredictability of cancer immunotherapy options. According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. MPEP 2164.04.

The examiner has not shown that administering a sufficient amount of a human cell line that is deficient in major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens and which has been modified to express a gene encoding an immunomodulator and a gene encoding an antigen of Epstein-Barr virus (EBV) will not induce or stimulate an immune response to an EBV-associated cancer as in pending claims 16-57.

The examiner has failed to establish a prima facie case of lack of enablement because the examiner has not shown why a skilled artisan would not be able to obtain a human cell line, that lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens and which has been modified to express (i) a gene encoding an immunomodulator and (ii) a gene encoding an antigen of Epstein-Barr virus (EBV).

The instant application, in some embodiments, provides compositions and methods relating to human cell lines that lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens and which have been modified to express an immunomodulator and an antigen of Epstein-Barr virus (EBV). Also provided by the present disclosure are methods of inducing or stimulating an immune response in a human to an EBV-associated cancer by administering one of the aforementioned compositions in an amount sufficient to induce or stimulate an immune response to the antigen of EBV expressed by the human cell line, whereupon an immune response to the EBV-associated cancer is induced. Thus, use of a bystander line, e.g., K562 obviates the need for *in vitro* passaging or modification, such as by transduction, of each patient's tumor cells, thereby guaranteeing a constant amount of cytokine production without any intra- or inter-patient variability, while utilizing the patient-specific antigenic repertoire.

The Examiner did not provide any evidence to show that generating a human cell line lacking MHC class I and class II antigens is not possible to practice the invention. To the contrary,

the specification provides an exemplary cell line (K562) and on paragraph [0018], the application describes methods to generate human cell lines that are deficient in expressing MHC class I and II antigens on cell surface. The specification also mentions SK-MEL-33 as a suitable cell line (paragraph [0017] of the specification). In addition, the specification describes interfering with the expression and/or transport of α-chain of MHC class I antigens and α-β chains of MHC class II antigens. The specification also provides examples to generate suitable cell lines by providing dominant negative forms of the respective antigens and by transfection, retroviral infection or homologous recombination to achieve expression of modified MHC or β_2 microglobulin genes or inactivation of genes.

Nevertheless, to expedite prosecution, claims 16-57 are amended to include K562 as a suitable cell line. Applicants reserve the right to pursue method claims involving cell lines other than K562 in continuing applications.

The specification provides adequate disclosure and guidance to enable a skilled artisan to practice claims 16-57. Applicants request the Examiner to withdraw the §112 rejections for claims 16-57.

V. Claims 1-4, 11-12, and 14-15 are Novel over Borrello et al.

On page 5 of the Office Action, the Examiner rejected claims 1-4, 11-12, and 14-15 as being anticipated by Borrello et al., (1999).

The Examiner mistakenly characterized Borrello to disclose the modified cell lines claimed herein. Borrello did not disclose a cell line transfected with plasmid *encoding* EBNA-1 as the examiner claimed. Instead, Borrello stated:

> The plasmid pCEP4hGM-CSF vector … contains the human GM-CSF gene under the regulation of a cytomegalovirus (CMV) promoter as well as the hygromycin resistance gene and the **EBNA-1 origin of replication** sequence.

Borrello, Page 1985, left column, under Gene Transfer section. (*emphasis added*).

Borrello does not teach a K562 cell line modified to contain a gene encoding an antigen of Epstein-Barr virus (EBV). The vector in Borrello has an EBNA-1 origin of replication and does not contain any portion of EBNA-1 coding sequence that would express an EBNA-1 antigenic region.

Therefore, Borrello does not disclose all the limitations of claims 1-4, 11-12, and 14-15 and applicants request the examiner to withdraw the §102(b) rejection.

VI. Claims 1-4 and 10-57 are Not Obvious Over Borrello et al., and Lee et al.

On pages 5-6 of the Office Action, the Examiner rejected claims 1-4 and 10-57 as being obvious over Borrello et al., (1999) and Lee et al., (1997).

As discussed in section IV, supra, Borrello does not teach "a universal K562 cell line transfected with plasmid encoding GM-CSF and EBNA-1 of an EBV antigen" as the Examiner alleged. Further, Borrello reports better results from "vaccination with a **mixture of autologous tumor cells** and an MHC-negative allogeneic GM-CSF-producing bystander cells" when compared to "using autologous tumor cells directly transduced to secrete GM-CSF". (Abstract). Borrello further states that their strategy "greatly simplifies further clinical development of autologous **tumor cell-based vaccines**." *Id.* (*emphasis added*). Borrello merely provides an alternate source for GM-CSF production—bystander cell line versus expressing within the tumor cells—for vaccines. Borrello neither suggests nor contemplates expressing an EBV antigen within the bystander cell line itself. Lee does not supply this missing limitation nor does a person of ordinary skill in the art can readily envision such a teaching.

Lee et al., (1997) describes some conserved CTL epitopes within EBV latent membrane protein 2 as a potential target for CTL-based tumor therapy. Specifically, Lee reported identification of five CTL target epitopes in LMP2 restricted through HLA alleles common in the southern Chinese population that is at risk for nasopharyngeal carcinoma. (Abstract). Lee described EBV-specific cytotoxic T lymphocytes (CTL)-based potential therapies for EBV-positive lymphomas. Id. Lee further states the requisites for a CTL therapy as follows:

> Recently there has been a great deal of interest in the prospect of using CTLs to treat human malignancies, but a prerequisite for any **CTL-based therapy** is the presence of an appropriate target Ag [antigen] **within the tumor cell**.

Lee, bridging paragraph, pages 3330-3331. (*emphasis added*).

Lee further speculates on possible CTL-based therapies:

> Alternatively, effective treatment may involve passive transfer of appropriate CTLs (grown under conditions that do not reduce their affinity for the target Ag).
>
> ***
>
> … administering pre-activated CTLs may prevent this [suppressive effect] problem.

Lee, page 3333, right column.

Thus, Lee merely describes possible CTL-based therapies that may have recognition of antigen expressed within the tumor cells. Lee does not even suggest using non CTLs as vaccines and further does not mention using a bystander line. As discussed earlier, Borrello was primarily

concerned with providing an alternate source for GM-CSF and involved mixing tumor cells with the bystander cells.

The combined teachings of Borrello and Lee do not render claims 1-4 and 10-57 obvious because:

(i) teachings of autologous tumor cells and patient-derived CTL-based therapies do not suggest an isolated human cell line that has been modified to lack MHC-I & II antigens and express an immunomodulator and an antigen of Epstein-Barr virus (EBV), and uses thereof;

(ii) the combined teachings of Borrello and Lee do not offer "a finite number of identified, predictable solutions" or "predictable variations" as required by *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1730 (2007); and

(iii) there was no reasonable expectation of success that providing a cell line that expresses both GM-CSF and an EBV-antigen would function against EBV-associated cancers.

The Examiner did not offer any credible scientific evidence as to why a skilled artisan would have found the pending claims obvious. Mere conclusory statements are not adequate.

> [R]ejections on obviousness cannot be sustained by **mere conclusory statements**; instead, there must be some **articulated reasoning with some rational underpinning** to support the legal conclusion of obviousness.' KSR at 1741. (*emphasis added*).

Therefore, applicants request the Examiner to withdraw §103 rejections for claims 1-4 and 10-57.

No other fees are due. However, please charge any fees that might be due in connection with this submission to our Deposit Account No. 12-0913 with respect to our matter number 43369-103949.

Respectfully submitted,

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